



(11) **EP 0 815 841 A1**

(12) **EUROPEAN PATENT APPLICATION**

(43) Date of publication:
07.01.1998 Bulletin 1998/02

(51) Int. Cl.⁶: **A61K 7/48**, A61L 15/20,
A61L 15/00

(21) Application number: **97202018.4**

(22) Date of filing: **02.07.1997**

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC
NL PT SE

(30) Priority: **05.07.1996 NL 1003524**

(71) Applicant: **Coöperatie Cosun U.A.**
4700 BH Roosendaal (NL)

(72) Inventors:
• **Vianen, Gerardus Maria**
4707 DZ Roosendaal (NL)

• **Meyer, Pieter Diederick**
4706 MH Roosendaal (NL)
• **Bink, Jacobus Petrus Maria**
4871 TA Etten-Leur (NL)
• **Walraven, Bastiaan Willem**
4707 SR Roosendaal (NL)

(74) Representative:
de Bruijn, Leendert C. et al
Nederlandsch Octrooibureau
P.O. Box 29720
2502 LS Den Haag (NL)

(54) **Composition for the prevention or treatment of nappy rash**

(57) The invention relates to compositions and products based on fabric, such as baby tissues, and based on composite materials, such as disposable nappies, which compositions and products are suitable for the prevention or treatment of nappy rash and nappy dermatitis. The active antimicrobial substances used according to the invention are one or more sugar fatty acid esters, the monoester content of which must be at least 30 %. The fatty acid component of the active substances is formed by one or more, saturated or unsaturated fatty acids having 6-22 carbon atoms, which fatty acids are straight-chain or branched and also can contain one or more hydroxyl groups. The sugar component of the active substances is, for example, sucrose, glucose, fructose, sorbitol or a mixture thereof. The above-mentioned active substances, which are completely harmless, are used in an amount of 0.01-15 % by weight in the composition or the product.

EP 0 815 841 A1

BEST AVAILABLE COPY

Description

The invention relates to compositions and products based on fabric, such as baby tissues, and based on composite materials, such as disposable nappies, which compositions and products are suitable for the prevention or treatment of nappy rash.

One of the most common skin problems in babies and toddlers relates to nappy rash, which is also termed nappy dermatitis. The studies cited in US-A 5 362 488, which were carried out on children younger than 2 years old, revealed that approximately two-thirds of the children were suffering from some form of nappy rash. For about 10 % of the children the nappy rash was rated as moderate, whilst for 5 % of the children the nappy rash was recorded as severe.

Up to now the urine and the faeces of the children have been regarded as the main causes of the development of nappy rash. According to US-A 5 362 488, faeces must be regarded as the main cause of nappy rash since nappy rash apparently occurs more frequently in the presence of faeces than in the presence of urine. Furthermore, it is reported in US-A 5 362 488 that nappy rash renders a child susceptible to irritation and infection, the two most common types of infection being related to yeasts and bacteria. The most common yeast infection is apparently caused by *Candida albicans* and the most common bacterial infection by *Staphylococcus aureus*. A similar combination of infections is also indicated in other literature. For example, the influential role of *Corynebacterium ammoniagenes* and *Staphylococcus aureus* on nappy rash is described in Barnett G., Baby Toiletries, Cosmetic Science and Technology, second edition, vol. 1, pp. 128-131, in Harry R., Harry's Cosmetology, Principles and Practice of Modern Cosmetics, 6th edition, vol. 1, pp. 540-542 and in Leyden J., Diaper Dermatitis, Dermatological Clinics, 1986, vol. 4, no. 1, pp. 23-28, whilst in Leyden J., (loc. cit.) an infection with *Candida albicans* is reported as a secondary effect.

US-A 5 362 488 proposes a buffered skin cream, which contains, inter alia, methylparaben and propylparaben as antimicrobial agents, for the prevention and treatment of nappy rash. However, it has been found that parabens are substances which are not harmless to man since these substances can lead to sensitisation. This sensitisation is expressed, inter alia, in chronic dermatitis, angio-oedema, hyperactivity, asthma, eczema and loss of sensation in the oral cavity. Furthermore, parabens are powerful histamine liberators (see E = eetbaar (E = edible), Dr. J. Kamsteeg & Ir. N.I.A. Baas, 3rd impression, Becht, Haarlem).

EP-A 0 613 675 describes cleaning cloths or tissues which contain an antimicrobial emulsion of low viscosity, which is suitable for controlling causative microorganisms in nappy rash. In addition to one or more bacterial preservatives such as parabens and chlorine-containing substances, such as 5-chloro-2-methyl-4-isothiazolin-3-one, the only specific antimicrobial agent mentioned is the compound cetylpyridinium chloride. This antimicrobial agent, which is said to act against microorganisms which play a role in nappy rash, such as *Staphylococcus* species and *Candida albicans*, cannot be regarded as harmless since quaternary ammonium compounds, such as said cetylpyridinium chloride, are not permitted as preservatives in the food industry (no E number).

Furthermore, disposable nappies which, in addition to a top layer and a backing, also contain a core layer, which core layer contains an antimicrobial agent in addition to an acid buffer, are described in EP-A 0 311 344. Once again, quaternary ammonium salts, such as the abovementioned cetylpyridinium chloride, are mentioned, inter alia, as examples of such an antimicrobial agent.

The aim of the invention is, firstly, to develop a composition which can be used to prevent or treat nappy rash and nappy dermatitis, which composition contains a substance harmless to man as antimicrobial agent.

Surprisingly, the abovementioned aim can be achieved if one or more sugar fatty acid esters are used as antimicrobial agent. This result is the more surprising in view of the fact that the sugar fatty acid esters concerned - certainly in lower concentrations - display no or virtually no action against other, skin-friendly, microorganisms belonging to the skin flora of man, such as *Micrococcus luteus* and *Staphylococcus epidermis*.

The invention therefore firstly relates to a composition for the prevention or treatment of nappy rash, which is characterised in that at least one or more sugar fatty acid esters are present therein as active antimicrobial substance.

The sugar fatty esters to be used as active substance in the compositions according to the invention can be prepared on the basis of a sugar such as sucrose, glucose, fructose or galactose or of a polyol such as sorbitol, mannitol, lactitol or xylitol, or of a mixture thereof, on the one hand, and saturated or unsaturated fatty acids having 6-22 carbon atoms, which fatty acids can be straight-chain or branched, on the other hand. Furthermore, the fatty acids can also contain one or more hydroxyl groups. Examples of suitable fatty acids are lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, hydroxy- and isostearic acid. A method of preparation for suitable sugar fatty acid esters is described, inter alia, in US Patent 4 778 881. Suitable sugar fatty acid esters can also be prepared by hydrolysis of such products. Specifically, hydrolysis of, for example, sucrose fatty acid ester leads to the formation of (a mixture of) glucose fatty acid esters and fructose fatty acid esters.

The sugar fatty acid esters in the compositions according to the invention must have a monoester content of at least 30 %, advantageously of over 50 % and more particularly of at least 70 %. In the case of 30 % monoesters, it can be stated that usually 40-70 % diesters and 0-30 % tri- or higher esters are also present in the sugar fatty acid ester product. The fatty acid component used in these esters can be one or more of, for example, the abovementioned fatty acids,

such as the combination laurate/palmitate, laurate/stearate or palmitate/stearate.

The sugar fatty acid esters are mild and non-irritant to human skin. Said esters are non-toxic, odourless and, under the conditions for use, unsusceptible or barely susceptible to hydrolysis. Furthermore, the sugar fatty acid esters can be regarded as harmless since, under the conditions for use, said esters - as far as is known - develop no action whatsoever which is harmful to man.

In the ready-to-use compositions, depending on the form thereof, the sugar fatty acid esters can be used in a wide range, for example in a range of 0.01-15 % by weight, advantageously 0.1-10 % by weight, and very particularly 0.1-5 % by weight, calculated on the basis of the total weight of the composition.

The compositions according to the invention can be produced in diverse forms, such as soaps, creams, lotions, sticks and the like.

Products based on fabric or based on composite materials also fall within the scope of the invention. In the context of the invention, fabric is understood to be woven or nonwoven material. Examples of fabric are materials based on textiles, such as cotton, for example cotton nappies, based on cellulose-containing material, such as paper, for example tissue paper, and based on synthetic fibres, which are used as the base material for, in particular, disposable nappies.

The active substances according to the invention can be incorporated or impregnated in the fabric as such or in the form of, for example, an emulsion. Examples of composite materials which may be mentioned in this context are, inter alia, disposable nappies, which in general are made up of a top layer, a backing and an intermediate layer, in which intermediate layer the active substances according to the invention are usually incorporated.

In addition to the active antimicrobial sugar fatty acid esters, the compositions and products according to the invention can also contain - depending on the embodiment - the active or non-active materials known from the prior art, such as buffers, cleansing agents, surface-active substances, emulsifiers and perfumes, as well as other active substances, such as lipase and protease inhibitors; see, for example, EP-A 0 117 613.

The invention is explained in more detail with the aid of the following example, which must not be interpreted as being restricting.

Example

MATERIAL AND METHOD

Harmful strains:

Corynebacterium ammoniagenes

ATCC* 6871

Staphylococcus aureus

ATCC 25923

Candida albicans

ATCC 14053

These strains were cultured in, respectively, Nutrient Broth (NB, Oxoid CM 1), Trypton Soya Broth (TSB, Oxoid CM 129) and YM Broth (Yeast, Malt, Peptone and Glucose - Difco 0711-170) and incubated at, respectively, 30, 37 and 30 °C. After checking for purity, they were frozen in liquid nitrogen (20 % glycerol).

NB plus 0.5 % glucose (NBglc) and Nutrient Agar (Oxoid CM 3) plus 0.5 % glucose (NAGlc) was used as common medium for the three strains.

Skin-friendly strains:

Micrococcus luteus ATCC 533

Staphylococcus epidermis ATCC 155.

The *Micrococcus luteus* strain was incubated at 30 °C and the *Staphylococcus epidermis* strain at 37 °C on TSB (Trypton Soya Broth: Oxoid CM 129). The two strains were tested for purity and then frozen in glycerol (20 %) in liquid nitrogen. In addition, the strains were kept on plate (TSBA medium; TSBA = Trypton Soya Broth (medium CM 129 from Oxoid Ltd) + 1 % agar) and further inoculated at regular intervals (at least once per week).

(*ATCC = American Type Culture Collection, Maryland 20852, USA)

Sugar fatty acid esters:

Sisterna® SP70 = 70 % stearate, 30 % palmitate - 70 % sucrose monoester.

Sisterna® L70 = 70 % laurate, 30 % palmitate - 70 % sucrose monoester.

For the harmful strains these sugar fatty acid esters were added to the NAglc medium in concentrations of 0, 400, 800, 1600 and 3200 mg/l (prepare highest concentration first and then dilute successively with NAglc medium) before sterilisation. After sterilisation (15 minutes at 120 °C) plates were poured therefrom, which plates were used to test the inhibitory action of these sugar fatty acid esters on the abovementioned strains.

For the skin-friendly strains the sucrose fatty acid esters were added to the TSBA medium in the abovementioned concentrations before sterilisation, after which the mixtures were sterilised for 15 minutes at 120 °C. The plate which was provided with a TSBA medium was then inoculated with 100 µl culture and incubated at the desired temperature (see above). For this purpose use was made of overnight cultures in TSB (= Trypton Soya Broth), which were inoculated undiluted (o.n.) and diluted 1:100.

Test method:

The test method used was the plate method. With this method the NAglc medium or the TSBA medium, as appropriate, was made up with the sucrose fatty acid ester solutions having the abovementioned concentrations. The abovementioned sugar fatty acid ester-NAglc plates were inoculated with 100 µl of the 1:50 dilution of overnight culture of the said harmful strains in the NBglc medium. The abovementioned TSBA plates were inoculated with 100 µl of undiluted overnight culture in TSB and 100 µl of a 1:100 dilution of overnight culture in TSB (Trypton Soya Broth = Oxoid CM 129) of the skin-friendly strains. The plates with *Corynebacterium ammoniagenes* and *Candida albicans* or *Micrococcus luteus* were then incubated at a temperature of 30 °C and the plates with *Staphylococcus aureus* or *Staphylococcus epidermis* at a temperature of 37 °C for 20-28 hours, after which the inhibition was assessed.

The inhibition obtained was related to the growth in the positive controls. The inhibition was categorised as 0, 0 to 20, 20 to 40, 40 to 60, 60 to 80 and 80 to 100 % inhibition.

The control used for the harmful strains was a blank determination in an NAglc medium without sucrose fatty acid ester solution.

The control used for the skin-friendly strains was a blank determination in a TSBA medium without sucrose fatty acid ester solution.

The results of the tests are given in Table A below.

TABLE A

Ester: conc. (ppm)	C. ammoniagenes 1:50	S. aureus 1:50	C. albicans 1:50	M. luteus		S. epidermis	
				O.n.	1:100	O.n.	1:100
SP70 400	++++	+++	0	0	+	0	0
800	++++	+++	0	+++	++++	0	0
1600	++++	++++	0	++++	++++	0	0
3200	++++	++++	0	++++	++++	0	0
L70 400	++++	++	+++	0	0	0	0
800	++++	++	+++	0	0	0	0
1600	++++	+++	++	0	+	0	0
3200	++++	++++	++++	+	+	0	0
Control 0	0	0	0	0	0	0	0

Legend:

0 = no inhibition,
 + = 0-20 % inhibition,
 ++ = 20-40 % inhibition,
 +++ = 40-60 % inhibition,
 ++++ = 60-80 % inhibition,
 +++++ = 80-100 % inhibition, with respect to control

SP70 = 70 % stearate, 30 % palmitate - 70 % sucrose monoester
 L70 = 70 % laurate, 30 % palmitate - 70 % sucrose monoester

Claims

1. Composition for the prevention or treatment of nappy rash, characterised in that the composition contains at least one or more sugar fatty acid esters as active substance.
2. Composition according to Claim 1, characterised in that the composition contains one or more sugar fatty acid esters having a monoester content of at least 30 % as active substance.
3. Composition according to Claim 2, characterised in that the composition contains one or more sugar fatty acid esters having a monoester content of at least 50 % as active substance.
4. Composition according to one or more of Claims 1-3, characterised in that the fatty acid component of the active substance is formed by one or more saturated or unsaturated fatty acids having 6-22 carbon atoms, which fatty acids are straight-chain or branched.
5. Composition according to Claim 4, characterised in that the fatty acids also contain one or more hydroxyl groups.
6. Composition according to one or more of Claims 1-5, characterised in that the fatty acid component of the active substance is lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, hydroxy- and/or isostearic acid or a mixture thereof.
7. Composition according to one or more of Claims 1-6, characterised in that the sugar component of the active substance is sucrose, glucose, fructose, galactose, sorbitol, mannitol, lactitol, xylitol or a mixture thereof.
8. Composition according to one or more of Claims 1-7, characterised in that the active substance is present in an amount of 0.01-15 % by weight, calculated on the basis of the total weight of the composition.
9. Products based on fabric, such as baby tissues, and products based on composite materials, such as disposable nappies, which can be used in the case of nappy rash, characterised in that the products concerned contain one or more sugar fatty acid esters which act as active substance, as defined in one or more of Claims 1-8.
10. Products according to Claim 9 which can be used in the case of nappy rash, characterised in that the active substance has either been impregnated into the product, such as a cotton nappy, or is present in one component of the composite nappy.
11. Method for controlling the microorganisms *Corynebacterium ammoniagenes*, *Staphylococcus aureus* and *Candida albicans*, which play a role in nappy rash, characterised in that a composition according to one or more of Claims 1-8 or a product according to Claim 9 or 10 is used on or in the immediate vicinity of the affected part of the skin.
12. Use of an active substance for the preparation of a composition or for the production of a product based on fabric or based on composite materials for use for the prevention or treatment of nappy rash, characterised in that one or more sugar fatty acid esters as defined in one or more of Claims 1-7 are used as active substance.



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 97 20 2018

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	WO 96 16681 A (PROCTER & GAMBLE) 6 June 1996 * page 22, line 18 - page 23, line 33; claims 1,6 *	1-12	A61K7/48 A61L15/20 A61L15/00
X	STN, File Supplier, Karlsruhe, DE, File XP002027636 Chemical Abstract, vol 117, nr 21939 zie samenvatting & JP 04 041 404 A (LION CORP.)	1-8	
X	AU 22748 77 A (MED-CHEM LABORATORIES) 7 September 1978 * the whole document *	1-8	
X,P	EP 0 750 903 A (COÖPERATIE COSUN UA) 2 January 1997 * the whole document *	1-8	
X	DATABASE WPI Section Ch, Week 7707 Derwent Publications Ltd., London, GB; Class D21, AN 77-11980 XP002027637 & JP 52 000 806 A (DAIICHI KOGYO KK) , 6 January 1977 * abstract *	1-8	TECHNICAL FIELDS SEARCHED (Int.Cl.8) A61K A61L
A	PATENT ABSTRACTS OF JAPAN vol. 14, no. 086 (C-690) & JP 01 299233 A (DAI ICHI KOGYO SEIYAKU CO) * abstract *	1-12	
A	US 5 231 087 A (THORNFELDT) 27 July 1993 * the whole document *	1-12	
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 3 November 1997	Examiner Fischer, J.P.
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

EPO FORM 1503 03/82 (P4/C01)

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☒ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.